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The Benefits of Intermittent Fasting on Patients with Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is the 7th leading cause of death in the United States, comprising about 10% of the population. With intermittent fasting gaining popularity in the media as a method to lose weight and control chronic illness, patients with diabetes would likely turn to any of the fasting methods in order to better manage their disease. However, there is a paucity of information to support whether intermittent fasting is an effective method to control diabetes, in conjunction with lifestyle modifications and anti-diabetic pharmacotherapy. This review sought to identify clinically relevant human studies that provide evidence that intermittent fasting is beneficial for those who suffer from type 1 or type 2 diabetes. A systematic review of the published literature was performed using PRISMA protocol in order to identify clinical trials that evaluated the effects of fasting in patients with type 1 or type 2 diabetes, specifically focusing on body weight (kg), hemoglobin A1C (%), and blood plasma glucose levels (mmol/L). Four randomized controlled trials and one case report of fasting in adults on anti-diabetic therapy with diabetes were identified. Improvements in weight, A1C, and/or fasting plasma glucose were identified in all of the studies. Patients may approach their health care providers with the desire to utilize fasting as an alternative to effectively manage their diabetes. Providers can use the studies included in this review as well as others that are available as a guide in order to make proper recommendations and monitor their patients safely. However, more studies should be performed in order to make accurate claims regarding the long-term effects of intermittent fasting among patients with diabetes.

KEYWORDS: *diabetes mellitus, intermittent fasting, alternate-day fasting, intermittent energy restriction, time-restricted feeding, intermittent dieting, periodic fasting*

INTRODUCTION

Fasting, an ancient practice, has recently gained popularity in mainstream media as a means to lose weight and control chronic illness^{1, 2}. Diabetes mellitus, affecting about 10% of the US population, is a chronic condition characterized by hyperglycemia due to insulin resistance or deficiency³. Diabetes may require intensive lifestyle modifications and/or pharmacological management, resulting in long-term end-organ damage if left untreated³. Any of the intermittent fasting (IF) regimens may seem attractive to patients with either type 1 or type 2 diabetes if typical anti-diabetic therapies become too costly, cause adverse effects, or fail.

IF describes eating patterns that cycle between feeding and fasting periods that specify when to eat, rather than what to eat, with the end goal of caloric restriction^{1, 2}. Common IF eating patterns include time-restricting feeding, in which energy intake is restricted for consecutive hours in a day, alternate-day fasting, in which energy intake is restricted every other day, and modified fasting, in which energy intake is restricted to any two or three days of the week^{1,3}.

Peer-reviewed human IF studies are limited while a majority of the information is written by health gurus or is based on rat studies¹. Several studies show that IF is effective for weight loss in overweight and obese adults⁴⁻⁷. Trial data on fasting patients with diabetes is scarce. A 12-week randomized control trial by Varady et al (2013) demonstrated a 6% decrease in fasting glucose levels in the alternate-day fasting group compared to the control group with no restrictions⁸. Another randomized control trial by Klempel et al (2012) showed reductions in glucose and insulin levels ($P < 0.05$) in an 8-week IF study⁶. Both studies had subjects with varying body mass indices (BMI 20-39.9 kg/m²) who were non-diabetic. These results show promise for the use of therapeutic fasting, but more studies should be performed in patients with diabetes to fully understand IF as a diet strategy.

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The objective of this systematic review is to utilize the limited data to provide recommendations on how to safely monitor patients with diabetes who want to try IF. Religious fasting regimens and animal studies will not be included.

METHODS

Database Search Strategy

A systematic review of the literature was performed using electronic databases for published, peer-review articles in English. Major databases that were used in this review were PubMed, Science Direct, CINAHL Plus, and Cochrane Collection Plus. Searches were performed using keywords “diabetes mellitus” in combination with either “intermittent fasting,” “alternate-day fasting,” “intermittent energy restriction,” “time-restricted feeding,” “intermittent dieting,” or “periodic fasting.” Reference lists of selected articles were also inspected due to the limited number of articles that resulted during the search. Titles of studies were critiqued by looking for any keyword combination. Of those selected, the “Methods” sections were screened using the inclusion and exclusion criteria (see section on “Inclusion and Exclusion Criteria”). The Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) protocol was used in order to determine which studies were eligible to be included in the review.

Protocol Used

PRISMA, composed of a flowchart and a checklist, is an organized method to improve the reporting quality of the papers included in this review⁹. The flowchart assists with the identification, screening, eligibility, and inclusion process for papers being reviewed. The 27-item checklist pertains to the quality of the content of a systematic review or meta-analysis, including the title, abstract, methods, results, discussion, and funding. A total of 376 records were identified through electronic database searches. The studies were compiled in a list and

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arranged in alphabetical order of the primary author. 79 duplicate studies were then removed by manually reviewing the list. 297 records were left to be screened for relevancy of the title and abstract (see “Inclusion and Exclusion Criteria” below). Of those, 267 papers were excluded due to irrelevancy, leaving 30 full-text articles to be assessed for eligibility. 25 of those studies were excluded for not meeting inclusion criteria, with a total of 5 studies included in the qualitative synthesis.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria across the final papers that were selected had several similarities. Inclusion criteria included adults over the age of 18 with type 1 or type 2 diabetes on anti-diabetic therapy with an A1C \geq 6.5%. Exclusion criteria included animal studies, religious fasting, pregnant and/or lactating subjects, and those with previous weight loss surgery. Studies in which fasting glucose results were unavailable were not excluded due to the paucity of data.

Setting and Subjects

In both the 2016 and 2018 Carter et al studies, the participants were recruited to the University of South Australia from the general population with the use of public advertisements^{10,11}. There were no differences of inclusion criteria between the two trials. Participants from the Corley et al (2018) study were recruited from secondary care diabetes clinics, local community networks, and primary care practices around New Zealand and then attended the Centre for Endocrine, Diabetes, and Obesity Research at Wellington Hospital¹². In the Furmli et al (2018) study, a chart review took place in the Intensive Dietary Management Clinic in Toronto, Canada, and was performed with the three case study patients who provided verbal and written consent to participate¹³. Lastly, the subjects in the Overland et al (2017) study were eligible to participate if they were adults with type 1 diabetes with a BMI of 25-40 who

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attended the Diabetes Centre at Royal Prince Alfred Hospital in Sydney, Australia¹⁴. Each study obtained approval from their own respective ethics committees and all subjects were provided informed written consent to proceed with the experiments.

RESULTS

Characteristics of subjects

Each study featured adult, overweight or obese subjects with preexisting type 1 or 2 diabetes that were being treated with anti-diabetic agents. Each study except one showed that the subjects had a starting BMI of ≥ 25 and a baseline A1C of $\geq 6.5\%$. The three case subjects in Furmli et al (2018) did not disclose their heights so BMI could not be obtained; however, initial waist circumference ranged from 89-123 cm and weight ranged from 61-97.1 kg¹³. Each of the subjects in the Furmli study also had comorbidities which included hyperlipidemia, hypertension, chronic kidney disease, and renal cell carcinoma¹³. Subjects in the other four studies did not have any diabetes-related organ damage or comorbidities other than overweight or obesity^{10-12,14}.

Recruitment/response

All five of the studies included in this review revealed similar findings, in that IF is associated with significant decreases in body weight, A1C, and fasting plasma glucose levels (Table 1). Decreases in body weight ranged from 3.3-13.3%¹⁰⁻¹⁴. In addition, all studies showed significant improvement in A1C levels, with Corley et al (2018) showing the largest decreases (-7.1% for the consecutive fasting group and -8.5% for the non-consecutive fasting group)¹². Corley et al (2018) also showed that IF was associated with a lower-than-expected and clinically acceptable risk of hypoglycemia, when combined with weekly supervision, hypoglycemia education, and medication reduction at baseline¹². The most notable outcome in Furmli et al

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(2018) is that all subjects discontinued their insulin use completely¹³. Fasting glucose results were only available in two studies, both showing significant decreases^{11,12}. Improvements in quality of life and enjoyment of the active participation in their diabetes management via fasting was also noted by subjects^{12,13}.

Table 1. Changes in body weight, A1C, and fasting glucose levels from baseline to end of studies.

Study	Type	N	Subjects	Treatment/Control	Body Weight	A1C	Fasting Glucose
Carter et al (2016) ¹⁰	Pragmatic pilot randomized trial	63	Adults; diagnosed with T2DM, on anti-diabetic medication BMI ≥ 27 Avg A1C 7.3%	Moderate continuous energy restriction	-5.9%	-0.7%	--
				2-day severe energy restriction w/ 5 days of habitual eating	-5.9%	-0.7%	--
Carter et al (2018) ¹¹	Randomized non-inferiority pilot study	97	Adults; diagnosed with T2DM, on anti-diabetic medication BMI ≥ 27 Avg A1C 7.3%	Continuous energy restriction diet	-5.0%	-0.5%	-11.8%
				Intermittent energy restriction diet	-6.8%	-0.3%	-11.8%
Corley et al (2018) ¹²	Randomized control trial	37	Adults; diagnosed with T2DM, on anti-diabetic medication BMI 30-45 Avg A1C 6.7-10%	Consecutive fast 2d/wk	-2.9%	-7.1%	-15.9%
				Non-consecutive fast 2d/wk	-3.3%	-8.5%	-12.2%
Furmler et al (2018) ¹³	Case report	3	Adults; diagnosed with T2DM, on anti-diabetic medication Initial waist circumference: 89-123 cm Initial weight: 61-97.1 kg	Alternating 24hr-fast 3d/wk	-13.3%	-0.2%	--
Overland et al (2017) ¹⁴	Randomized parallel group pilot study	10	Adults; diagnosed with T1DM, on insulin BMI 25-40 Avg A1C 6.5-10%	Continuous moderate energy restriction: -30% relative to weight maintenance energy needs	-3.9%	-0.1%	--
				Severe energy restriction: 2d/wk	-7.0%	-0.0%	--

DISCUSSION

Main Findings

These studies show that when individuals with type 1 or type 2 diabetes on anti-diabetic medications incorporate IF into their lifestyle, statistically significant decreases in body weight, A1C, and fasting blood glucose occur (see Table 1). When comparing intermittent energy restriction to continuous energy restriction, as in Carter et al (2016 and 2018) and Overland et al (2017), decreases in body weight and A1C are similar^{10,11,14}. This suggests that any of the IF regimens could serve as a viable option for losing weight and lowering blood sugar levels. IF may increase patient adherence since the primary focus is *when* to eat, as opposed to continuous energy restriction, or caloric restriction, which limits the amount of calories eaten each day. In the Corley et al (2018) study, there were no differences in the results between the consecutive and the non-consecutive 2-day per week fast¹². This suggests that a patient may fast everyday or every other day and achieve the same results, depending on preference.

Comparison of Findings with those Reported in the Literature

A systematic review by Horne, Muhlestein, and Anderson¹⁵ showed that fasting was associated with improvements in weight and other cardiovascular and metabolic parameters, such as triglycerides, LDL-cholesterol particle size, and C-reactive protein. Patient populations of each study varied including individuals who were healthy, obese, elderly, or had a diagnosis of coronary artery disease or diabetes. Improved mood was also reported in two randomized control trials. The overall results of the review seem promising in decreasing the risk of cardiovascular disease, diabetes, and mental health conditions, but further studies need to be performed on a larger scale to make more accurate claims.

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Strengths and Limitations

A limitation of this study is the scarcity of published literature regarding IF and its effects in persons with diabetes. The fact that all of the studies identified in this review were published within the last 4 years indicates this is an area of active interest and ongoing research. While current, these studies are limited to populations in Australia, New Zealand, and Canada and may not be generalizable. Another limitation is differences in the length of treatment for each study, ranging from 12 weeks to 12 months. In addition, Furmli et al (2018) and Overland et al (2017) had the smallest sample sizes, undermining the external validity of this review. Furthermore, only one study involved subjects with type 1 diabetes while the other four studies had subjects with type 2 diabetes.

Implications for Research

Future studies should take place in other countries for longer durations with larger sample sizes. Collectively, these factors would help the data to be more generalizable and allow clinicians to make more comprehensive recommendations for long-term fasting. More patients with type 1 diabetes should be included so that proper guidelines can be made with regards to fasting, insulin use, and the risk for hypoglycemia.

Implications for Clinical Practice

Educating patients on the benefits of IF may help control diabetes and wean the use of oral or injectable anti-diabetic agents. Fasting might be appealing to patients who are averse to taking medication and wish to avoid side effects. Medications can also be very costly, and IF is an inexpensive intervention that can be done in a variety of ways, allowing patients to choose how they fast based on personal preference. Since IF is a popular diet, providers need to know the risks and the benefits before counseling and managing patients.

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In order for health care providers to optimally monitor patients with diabetes during fasting, they should seek guidance from peer-reviewed articles. The American Diabetes Association (ADA) does not have specific recommendations for patients with diabetes who want to try IF. However, an article written by Al-Arouj et al (2010) released by the ADA provides recommendations for religious fasting among patients with diabetes¹⁶. To avoid the risk of hypoglycemia, the article stresses the importance of individualized treatment plans, frequent blood glucose checks, and proper exercise and nutrition. Al-Arouj et al makes specific recommendations regarding medication adjustments, depending on the type of anti-diabetic medication the patient is taking¹⁶. Providers can use this article as a starting guide, as well as another article by Grajower & Horne, which makes similar recommendations regarding medication adjustments, but specifically for various IF regimens¹.

With proper counseling and monitoring by health care providers, patients with diabetes can live longer, healthier, and happier lives through fasting. Though these results seem reassuring, future studies should be performed in order to provide proper recommendations regarding the long-term effects of IF among patients with diabetes.

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